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Treatment of hypertension: State of the art in 1979

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Summary

1. The results of the Veterans Administration Co-operative Study have been extended by the subsequent clinical trials, which included patients of both sexes and with less vascular disease. The later studies confirm the effectiveness of treatment in preventing most complications except myocardial infarction and sudden death. Furthermore, the lower diastolic blood pressure in which treatment has been shown to have a significant beneficial effect has been lowered from 105 mmHg as indicated by the Veterans Study to 100 mmHg as shown by the much larger Australian trial. The possibility of reducing the incidence of sudden death and fatal myocardial infarction has been suggested by other recent control trials using β-adrenoreceptor-blocking drugs, an approach that needs further exploration.

2. A number of interesting and useful new drugs have appeared which include tienilic acid, minoxidil, saralasin and captopril, and in addition recent controlled trials have re-emphasized the effectiveness of the old drug, reserpine, when combined with a diuretic. The art of treatment of hypertension therefore appears to be in a healthy state and we should expect more advances in the future.

Key words: antihypertensive drugs, hypertension, treatment of hypertension.

Introduction

The last decade has been marked by revolutionary changes in the approach to the treatment of hypertension. Physician's attitudes have changed from a basically nihilistic view to one of therapeutic optimism. What are the reasons for this complete turn-around? Basically they are four; firstly, Kannel, Schwartz & McNamara (1969) and Kannel, Wolf, Verter & McNamara (1970) in the Framingham study and other epidemiological investigations have shown that hypertension of any degree increases the risk of death and the degree of risk increases directly in proportion to the height of the blood pressure. Secondly, the controlled therapeutic trials such as the Veterans Administration Cooperative Study Group (1970, 1972) and Smith (1977) have demonstrated conclusively that control of blood pressure with antihypertensive agents significantly reduces the risk of all complications except those associated with coronary artery disease. Thirdly, health surveys in various countries such as the United States Public Health Service National Health Survey (1966) demonstrated that definite hypertension (i.e. >160 systolic or >95 mmHg diastolic) affects about 15% of the adult population, the prevalence being lower than this in the young and much higher in the aged. Fourthly, private and public campaigns to educate the public and the profession on the importance of recognizing and treating hypertension have proliferated in many countries of the world in recent years.

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Effectiveness of treatment

How effective is antihypertensive drug treatment? Is it an unqualified success or are there limitations? The Veterans Administration Cooperative Study (1970, 1972) is a good starting point in examining these questions. The study contained 523 patients who were randomly assigned double-blind to either active drugs (thiazide plus reserpine plus hydrallazine) or to placebos. The study was terminated after an average follow-up of only 20 months in the patients with diastolic pressures in the range 115–129 mmHg before randomization. This was because of a marked difference in major cardiovascular complications with an incidence of 27 in the placebo group versus one in the treated patients. Four of the 27 cardiovascular events in

the control group were fatal whereas there were no cardiovascular-related deaths amongst the treated patients.

In the remaining 380 patients with initial diastolic blood pressures in the range 90–114 mmHg who were followed longer, there were 19 cardiovascular deaths in the control group versus eight in the treated. The cumulative incidence of major complications (either fatal or non-fatal) was extrapolated over a 5 year period using the life-table method of analysis. The incidence was 56% in the control group compared with 18% in the treated patients, a difference of approximately 3 to 1. However, significant benefit of treatment was limited to the patients with moderate hypertension and blood pressures of 105–114 mmHg. In the subgroup with moderate hypertension the ratio of major complications between the untreated and the treated patients was 4 to 1, a highly significant difference. In the patients with mild hypertension the ratio of morbid events was only 1·6 to 1, which was not significant. It appeared therefore that the higher the diastolic blood pressure the more effective were the results of treatment and that below 105 mmHg significant benefit could no longer be demonstrated.

Assessment of the efficacy of treatment in preventing specific complications revealed that such morbid events as congestive heart failure, accelerated forms of hypertension and progressive renal damage occurred only in the control group and were completely absent in the treated patients. The incidence of stroke also was markedly reduced. However, the occurrence of complications related to coronary artery disease such as myocardial infarction, sudden death, heart block and atrial fibrillation were essentially the same in the treated and control groups. These results suggest that complications related directly to hypertension, *per se*, are prevented but complications secondary to coronary artery disease are not affected by antihypertensive treatment. This observation may explain in part why treatment was less effective in mild hypertension because when these patients develop complications they are usually secondary to coronary artery disease rather than to other complications associated with hypertension.

The negative results with respect to coronary artery disease observed in the Veterans Administration Study must be regarded with some reservations because of the type of patients chosen for the study. Their average age was approximately 50 years; they were all men and most importantly nearly two-thirds had clinical evidence of target organ disease at the time of entry. If the trial had included more patients with early hypertension, in a younger age group and an equal mix of both sexes would the results have been different?

The Public Health Service Hospitals Trial in the United States (Smith, 1977) excluded patients with any signs of target organ disease. The average blood pressure was 144/99 mmHg and the average age was 44 years. Both males and females were included. The study group consisted of 389 patients randomly assigned to drug or placebo and the follow-up was 7 years. Because they were a considerably lower-risk group the complications were fewer than in the Veterans Administration trial. The conclusions, however, were essentially similar. Although definite benefit was demonstrated it was mostly in the prevention of hypertensive complications, not in the prevention of atherosclerotic events. As in the Veterans Administration study there was no essential difference between control and treated patients in the incidence of myocardial infarction. However, the total number of heart attacks observed during the study was too low to draw any definitive conclusions.

In a Report in this Symposium Dr Ralph Reader (Reader, 1979) has presented the results of the Australian trial on the effectiveness of treatment in patients with diastolic blood pressure in the range 95–109 mmHg. This massive and important study again bears out the essential conclusions of the Veterans Administration trial. Treatment was highly effective in moderate hypertension except for the prevention of myocardial infarction and sudden death. There is one important difference between the two studies, however. The Australian study, based on far greater numbers of asymptomatic patients, has extended the diastolic blood pressure where treatment was proved to be effective from 105 mmHg as found by the Veterans study to 100 mmHg in the Australian study. Only in the group with diastolic pressures below 100 mmHg did they fail to observe any benefit of treatment. Although the difference between 105 and 100 mmHg diastolic may seem insignificant it should be remembered that the great majority of hypertensive patients display diastolic pressures in the lower ranges and that the spread of 100–104 mmHg includes a large segment of the hypertensive population.

The present 'state of the art' with respect to indications for treatment, therefore, would appear to be the following. (1) There is a good agreement that treatment is effective in preventing many

hypertensive complications in patients with moderate and severe hypertension but not in mild hypertension. The diastolic blood pressure which determines whether benefit will be achieved or not appears to be approximately 100 mmHg. (2) The complications that stubbornly resist the effects of antihypertensive treatment are those associated with coronary artery disease, the most important of which are myocardial infarction and sudden death.

β-Adrenoreceptor-blocking drugs

The failure to prevent heart attacks by antihypertensive treatment alone has led to a search for other approaches to the problem. There have been two small controlled trials, by Almark, Saetre & Korsgreu (1974) and by Wilhelmsson, Vedin, Wilhelmsen, Tiblin & Werkö (1974), with alprenolol to prevent reinfarctions in patients who have already sustained a myocardial infarction. Both studies reported a significant decrease in sudden deaths in the treated patients as compared with the placebo group and the former but not the latter study found a decrease in the number of reinfarctions. The Multicentre International Study Group (1975) conducted a large study in post-infarction patients with practolol. The study was terminated prematurely because of the reports of drug toxicity. However, results for approximately 3000 patients followed for several months to several years indicated that the practolol-treated group showed a significant reduction in cardiac-related deaths, including sudden death, although the reinfarction rate was not significantly different in the treated versus the control groups. The protective effect of practolol was most evident in patients with anteriorly located pre-entry infarcts and whose blood pressures at entry were in the normotensive range. These studies are encouraging but are not conclusive, particularly as they included normotensive as well as hypertensive patients and were either small in size or brief in duration.

The β-adrenoreceptor-blocking agents represent a major advance in antihypertensive drug treatment. The subjective side-effects are minimal and those in current use have a good safety record if they are prescribed with discretion. Blocking agents with slightly differing properties have been developed. These include the cardioselective agents and the blocking drugs with sympathomimetic properties. The cardio-selective agents such as atenolol or metropolol have had the greatest clinical acceptance. They appear to be somewhat better tolerated in patients with bronchitis or chronic obstructive pulmonary disease without a prominent bronchospastic component.

The most widely used β-adrenoreceptor-blocking agent has been propranolol. The Veterans Administration Cooperative Study Group on Antihypertensive Agents (1977) evaluated the effectiveness of this agent when given alone or in combination with a thiazide and/or hydrallazine in patients with initial diastolic pressures averaging between 90 and 114 mmHg. Hydrochlorothiazide plus reserpine was used as the reference treatment. The various regimens were randomly assigned double-blind to 450 patients with pre-randomization average diastolic blood pressures in the range 90–109 mmHg. Propranolol was titrated, the highest dose being 480 mg/day. Effectiveness was judged by the percentage of patients whose diastolic blood pressure was reduced to below 90 mmHg and which was at least 5 mmHg below the pre-randomization average pressure.

Propranolol alone was the least effective regimen reducing the diastolic blood pressure to goal levels in 52% of the patients. Propranolol plus hydrallazine (105 mg/day) controlled the blood pressure in 72%. Both of these regimens were significantly less effective than the other three combinations. The percentage of patients reaching goal diastolic blood pressure with the latter regimens were 81% with propranolol plus hydrochlorothiazide, 88% with reserpine (0·3 mg/day) plus hydrochlorothiazide and 92% with the triple drug regimen of propranolol, hydrochlorothiazide and hydrallazine.

As would be expected considerably higher doses of propranolol were used in the less-effective than in the more-effective regimens. Amongst the group of patients who received propranolol alone only 26% achieved control of their blood pressure with doses of 120 mg/day or less. By contrast 71% who took the three-drug regimen were controlled with low doses of propranolol. These results indicated clearly that adjunctive therapy, particularly thiazide diuretics, not only increases the effectiveness of propranolol but also reduces the dosage requirement.

Reserpine

It is noteworthy that the reserpine/hydrochlorothiazide combination was nearly as effective as the three-drug regimen and was more effective than either propranolol plus hydrochlorothiazide or propranolol plus hydrallazine. Other controlled trials in the U.S.A. have also demonstrated the effective-

ness of reserpine/diuretic combinations. For example, Grimm (1978), in evaluating the antihypertensive effectiveness of various drugs in the present multiple-risk-factor intervention trial against coronary heart disease (MRFIT programme) found that a reserpine/diuretic combination was significantly more effective in reducing blood pressure than was α-methyldopa plus a diuretic. In both this study and the Veterans Administration trial the reserpine/diuretic combination was associated with no more side-effects than the other regimens. Reserpine/diuretic combinations are inexpensive and easy to administer. It must be admitted that some individuals cannot tolerate reserpine, but careful selection of patients should reduce the number of serious side-effects such as depression.

Tienilic acid

Another recent trial by the Veterans Administration Cooperative Study Group on Hypertensive Agents (1979) has been concerned with the evaluation of ticrynafen or tienilic acid, a new uricosuric diuretic. This study involved 240 patients with mild hypertension. The treatments, which were randomly assigned, double-blind, consisted of two doses of ticrynafen (250 or 500 mg/day) as compared with two doses of hydrochlorothiazide (50 or 100 mg/day).

All four regimens lowered blood pressure significantly. The percentage of patients achieving diastolic blood pressures below 90 mmHg was 40% with the 250 mg dose of ticrynafen, 54% with the 500 mg dose and 51 and 57% respectively with the low and high doses of hydrochlorothiazide. Serum uric acid concentrations fell to approximately half of their pretreatment values in the ticrynafen-treated patients and rose with hydrochlorothiazide. Other biochemical side-effects including a reduction in serum potassium concentration were similar with ticrynafen and hydrochlorothiazide.

Minoxidil

Minoxidil is a relatively new vasodilator drug, which was shown by Limas & Freis (1973) to be of great value in the treatment of severe, drug-resistant hypertension including patients with renal failure. The drug is remarkably effective in controlling the blood pressure even in patients who were formerly resistant to every other antihypertensive agent either alone or in combination. It does not induce orthostatic hypotension, which is a great benefit in patients with renal failure, who exhibit marked fluctuations in extracellular volume associated with intermittent haemodialysis. There is a tendency to fluid retention, which needs to be controlled, and to tachycardia, which can be prevented with β-adrenoreceptor-blocking drugs. A frequent and sometimes distressing side-effect is hirsutism, particularly when it occurs in women.

Angiotensin inhibitors

Saralasin represents a new type of antihypertensive agent. It is a competitive antagonist of angiotensin II in vascular smooth muscle. Unfortunately its duration of action is brief and it is not effective when given orally. Because of these properties it is not useful as a therapeutic agent. Hollenberg, Williams, Adams, Moore, Brown, Borucki, Leung, Bavli, Solomon, Passan & Dluhy (1979) found that saralasin is useful in identifying patients with renin-dependent hypertension, including renovascular hypertension.

Another new agent affecting the renin–angiotensin system is captopril, which has been studied by Brunner, Gavras, Waeber, Kershaw, Turini, Vukovich, McKinstry & Gavras (1979). This drug inhibits the action of the enzyme which converts angiotensin I into angiotensin II. The angiotensin-converting enzyme, however, also prevents the metabolic breakdown of bradykinin, thereby increasing the concentration of bradykinin in the blood vessels. At present it is not certain whether the antihypertensive effect of captopril is due to reduction in angiotensin II, to an increase in bradykinin or to some other still unknown mechanism. The drug is effective in reducing blood pressure, particularly when combined with a diuretic, and its effectiveness does not seem to be limited to patients with high-renin hypertension. Side-effects have included skin rash and proteinuria. Although its final place in the therapeutic armamentarium of antihypertensive drugs has not yet been determined captopril represents an interesting new addition to the growing number of effective agents.

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